REMARKS

I. Status of Claims

Claims 4-19, 22-26, and 28 are pending in this application. Claims 16-19, 22-25, and 28 are withdrawn. Claims 4, 5, 7-14, 16-19, 26, and 28 have been amended. Claims 1-3, 20-21, 27, and 29-31 are canceled. The amendment introduces no new subject matter. By way of example, page 2, lines 20-22 of the specification indicates that NMB1870 is the art recognized designator for 741 by virtue of having been published in Tettelin *et al.* (2000) *Science* 287:1809-1815. By way of example, page 5, lines 6-8 of the specification indicates that NMB2091 is the art recognized designator for 936 by virtue of having been published in Tettelin *et al.* (2000) *Science* 287:1809-1815. By way of example, page 5, lines 21-23 of the specification indicates that NMB1030 is the art recognized designator for 953 by virtue of having been published in Tettelin *et al.* (2000) *Science* 287:1809-1815. By way of example, page 6, lines 4-6 of the specification indicates that NMB2132 is the art recognized designator for 287 by virtue of having been published in Tettelin *et al.* (2000) *Science* 287:1809-1815.

II. Election/Restrictions

Applicants respectfully request that the Examiner withdraw the designation of claims 16-19 and 22-25 as withdrawn. As presently amended, the claims all depend from claim 4 which is the elected invention of Group II.

III. Specification

The Examiner has objected to the specification based upon the use of the trademark TWEEN on pages 15 and 18. Applicants have amended the specification and therefore respectfully request that the Examiner withdraw the objection to the specification.

IV. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 1, 4-14 and 26 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicants respectfully traverse the rejection and its supporting remarks. The Examiner has not established a *prima facie* case of failure to comply with the written description requirement. The specification must be taken as complying with the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). The Examiner has not provided any reason to doubt that the specification fails to provide an adequate written description of the presently claimed invention. Instead, the Examiner has analyzed the claimed invention for compliance with the written description without first establishing a *prima facie* case, which would then require such an analysis.

There is sufficient written description

Even assuming that the Examiner has made a *prima facie* case for written description (which is traversed), the rejection is still successfully rebutted by the specification as filed in view of the state of the art at the time of filing.

The MPEP 2163(a)(1) makes clear that:

> "'(1) examples are not necessary to support the adequacy of a written description requirement; (2) the written description standard may be met … even where actual reduction to practice of an invention is absent; and (3) ***there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure***.' *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006). See also *Capon* v. *Eshhar*, 418 F.3d at 1358, 76 USPQ2d at 1084 ('The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes' ***where the genes were novel combinations of known DNA segments***.')"

The MPEP 2163(a)(1) makes clear that, "[w]hat is conventions or well known to one of ordinary skill in the art need not be disclosed in detail." Citing to *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). As the specification makes clear, the proteins that are presently claimed as combinations are known proteins. The specification on page 2, line 24 through page 6, line 20, provides a good summary these five antigens. By way of example as indicated on page 2, line 25 through page 3, line 18, NadA has been described including

alignments showing conserved regions, expression of variants and fragments have been explored, etc. Furthermore, many allelic variants of NMB1870 (741) have been disclosed. The specification cites to two sources on page 3, lines 30-31, one of which provides 22 sequences and the other of which disclosed 23 sequences.

Thus, the present invention is directed to combinations of known polypeptides much like *Capon* referred to in the MPEP which was a combination of two known proteins. Since one point of novelty is in the combination of the particular antigens, not the polypeptides in and of themselves, the specification does not need to describe these antigens to the same level as would be required for claims to novel polypeptides. But, as discussed above, the specification does provide a good summary of the state of the art with regard to each antigen and provides a number of references such that one of skill in the art would recognize that the inventors had possession of the claimed invention to the combination of five antigens.

Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 4-14 and 26 under 35 U.S.C. § 112, first paragraph, written description.

V. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 4 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy the written description requirement for the recitation of the designations "NadA" protein, "741" protein, "936" protein, and "953" protein, and "287" protein.

Applicants respectfully traverse the rejection and its supporting remarks. Use of a laboratory designation does not render a claim indefinite. The determination of what is definite does not depend upon whether the laboratory designation conveys structural or functional limitations that are described in the specification. One of skill in the art is deemed to read claims in light of the art and in light of the specification. In the case where a designation is not art recognized, one of skill in the art could readily refer to the specification and have no confusion as to the metes and bounds of the claimed invention given that there is a clear correspondence between the claimed designations and the art recognized designations.

However, in order to facilitate prosecution in this case applicants have amended the pending claim, without prejudice or disclaimer, to replace "741" with "NMB1870," to replace "936" with "NMB2091," to replace "953" with "NMB1030," and to replace "287" with "NMB2132." Applicants have not replaced "NadA" as the Examiner's citation to Comanducci *et al.* clearly demonstrates that NadA is an art recognized designation as it is used in a publication. With the amendment, the claim uses what are clearly art recognized designators of the antigens presently claimed and therefore one of skill in the art would have no difficulty understanding these terms. By way of example, page 2, lines 20-22 of the specification indicates that NMB1870 is the art recognized designator for 741 by virtue of having been published in Tettelin *et al.* (2000) *Science* 287:1809-1815. By way of example, page 5, lines 6-8 of the specification indicates that NMB2091 is the art recognized designator for 936 by virtue of having been published in Tettelin *et al.* (2000) *Science* 287:1809-1815. By way of example, page 5, lines 21-23 of the specification indicates that NMB1030 is the art recognized designator for 953 by virtue of having been published in Tettelin *et al.* (2000) *Science* 287:1809-1815. By way of example, page 6, lines 4-6 of the specification indicates that NMB2132 is the art recognized designator for 287 by virtue of having been published in Tettelin *et al.* (2000) *Science* 287:1809-1815.

Applicants respectfully request that the Examiner withdraw the rejection of claim 4 under 35 U.S.C. § 112, first paragraph.

VI. Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 4-14 and 26 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to enable the claims to their full scope.

Applicants respectfully traverse the rejection and its supporting remarks. Applicants respectfully traverse the rejection and its supporting remarks. The Examiner has not established a *prima facie* case of lack of enablement. The specification must be taken as complying with the first paragraph of § 112 unless there is a reason to doubt the objective truth of the statements relied upon therein for enabling support (*In re Marzocchi*, 169 USPQ 367 (CCPA 1971)). The Examiner has not provided any reason to doubt that the presently claimed invention is adequately disclosed so as to allow one of skill in the art to make and use the claimed invention. Instead, the Examiner

immediately begins with a discussion of the Wands factors without establishing that an analysis under the Wands factors is appropriate.

In discussing the Wands factors, the Examiner first cites to Bowie *et al.* for the assertion that three dimensional structure is unpredictable. This citation fails for two reasons. First, this paper was published in Mar. 1990 and therefore is discussing the state of the art more than ten years earlier than the priority date of the present application. Second, this paper is discussing an *ab initio* study of protein structure and function based solely upon the amino acid sequence, which is not relevant to the present situation. The relevant characteristic is immunogenicity, which is a well characterized characteristic. Furthermore, Wells (submitted herewith) teaches that there was a significant degree of predictability even as of 1990. For example, Wells on page 8515, right column, first paragraph of conclusions state that, "[I]n the majority of cases, combinations of mutations that affect substrate or transition state binding, protein-protein interactions, DNA-protein recognition, or protein stability exhibits simple additivity." In fact, Wells concludes his paper with the following paragraph:

> Simple additivity reflects the modularity of component amino acids in protein function. This results from the fact that the perturbations in energetics and structure resulting from most mutations are highly localized. In the past six years, an additive mutagenesis strategy has been ***extremely effective in engineering proteins*** – of course, nature has been using this strategy much longer.

Thus, Wells actually teaches that there was a high degree of predictability sufficient to allow engineering of proteins even in complex areas such as protein-protein interactions, DNA-protein recognition and protein stability. If such complex interactions were sufficiently predictable in 1990, then immunogenicity which was better characterized and much more robust is even more predictable.

The Examiner then cites to Greenspan *et al.* to support the assertion that defining an epitope is difficult. The claims are not directed to particular epitopes and do not require definition of epitopes for one of skill in the art to make and use the claimed invention. In this case, the key is the cross-reactivity of the antigens included in the mix. One of skill in the art can readily review the information in the art which includes sequence alignments such as that found in Comanducci *et al.*

to determine which areas of a given protein are conserved and therefore one of skill in the art would be less likely to manipulate in order to maintain the cross strain coverage.

Thus, the references cited by the Examiner could not be used to establish a *prima facie* case of lack of enablement.

There is sufficient enablement

Even if the Examiner had established a *prima facie* case of lack of enablement, the claims are sufficiently enabled.

The Examiner appears to be basing the entire lack of enablement rejection upon an assertion that epitopes are unpredictable and therefore undue experimentation would be required. Even if the Examiner is correct, lack of predictable results is not by itself sufficient to support a lack of enablement rejection. In the classic case on enablement, *In re Wands*, the court was asked to determine whether claims that required production of antibodies to a newly discovered antigen where only a single antibody had been isolated were enabled. The court held that the claims were enabled even though one of skill in the art could not predict the sequence of even a single antibody that could bind to the antigen other than the one that had been identified. The court looked at the nature of the art and the techniques involved in isolation of antibodies and determined that the scope of an "experiment" was not merely generating and testing a single hybridoma, but rather isolating several hybridoma and screening through them to see whether any produced antibodies that bound to the antigen, which at the time was very difficult and time consuming, but given the high skill in the art, the invention was still enabled. In this case, while the work may be time consuming, all of the techniques are routine techniques of molecular biology and immunology to construct and test modified antigens to determine which produce an immune response to the parent antigen.

Even if the Examiner is correct that there is unpredictability, all of the other *In re Wands* factors support the enablement. The application provides quite a bit of guidance by citation to what is known in the art about the individual proteins including sequence alignments of multiple variants (see, e.g., page 2, line 24, through page 6, line 20. It is well established that a specification does not need to include that which is old. The skill in the art is high as noted by the Examiner. The skilled

artisan is at least a graduate level researcher with experience in molecular biology and immunology. The nature of the invention is reasonably simple as any experimentation only requires application of routine techniques of molecular biology to generate and express mutated variants. Screening for immunogenicity is similarly routine. The specification starting on page 33, line 20, provides an examples of testing combinations of recombinantly expressed antigens for immunogenicity with comparisons to other compositions such as OMVs. Thus, the specification provides guidance in the form of an actual working example. Thus, undue experimentation would not be required and therefore the claimed invention is enabled.

Applicants respectfully request that the Examiner withdraw the rejection of claims 4-14 and 26 under 35 U.S.C. § 112, first paragraph, enablement.

VII. Rejection under 35 U.S.C. § 112, second paragraph

Claims 5, 7, 9, 11 and 13 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention for the recitation of "identity."

Applicants respectfully traverse the rejection and its supporting remarks. The determination of what is definite depends upon whether one of skill in the art would understand the metes and bounds of the claim. One of skill in the art is deemed to read claims in light of the art and in light of the specification. The Examiner has asserted that one of skill in the art would be confused by the term "identity" when used in the context of the claims requiring the protein has 85% or more "identity" to a cited sequence. The Examiner has not provided any evidence of even a single alternate use of the term "identity" in the context of a percentage in the art that would leave one of skill in the art confused as to the reasonable interpretation of the term. Applicants are unaware of any such alternative interpretation. However, in the interest of advancing prosecution, Applicants have amended the claims without actually changing the scope or interpretation at all by introducing "sequence" before the word identity.

Applicants respectfully request that the Examiner withdraw the rejection of claims 5, 7, 9, 11, and 13 under 35 U.S.C. § 112, second paragraph.

VIII. Rejection under 35 U.S.C. § 103(a)

Claims 4-14 and 26 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Fraser *et al.* (WO 99/57280, 1999) in view of Commanducci *et al.* (J. Exp. Med., 195:1445-1454, 6/2002).

Applicants respectfully traverse the rejection and its supporting remarks. Contrary to the Examiner's assertion neither of the two cited references teach that any of the polypeptides disclosed in either when administered to an individual would result in the claimed "antibody response is bactericidal against two or more of hypervirulent lineages A4, ET-5 and lineage 3 of *N. meningitidis* serogroup B." The Examiner has asserted that Comanducci *et al.* teach that allele 3 of NadA has such function. However, this is not accurate. The abstract of Comanducci *et al.*, as cited to by the Examiner, only indicates that the ET5 and cluster A4 strains have the NadA gene. Comanducci *et al.* only demonstrate that NadA (allele 3) as an antigen generates bactericidal antibodies against four particular strains (See Table II). As can be seen in Table I, only two of the strains are *N. meningitidis* serogroup B as is presently claims. Comanducci *et al.* teaches that one of the two strains, MC58, is listed as being in clonal group ET5. The other, 2996, was not assigned to a clonal group. Thus Comanducci *et al.* do not teach the claimed bactericidal activity. Furthermore, as shown in Table 1 of Giuliani *et al.*, NadA did not produce bactericidal antibodies against NZ98/254, which Giuliani *et al.* teach in Figure 1(c) as being lineage 3. Thus, there is affirmative evidence that NadA by itself does not produce bactericidal antibodies against at least one lineage 3 *N. meningitidis* serogroup B strain. Fraser *et al.* do not teach the claimed bactericidal activity. Thus, neither Comanducci *et al.* nor Fraser *et al.* teach all of the elements of the presently claimed invention. Since the cited references fail to teach all elements as claimed, the Examiner has not established a *prima facie* case of obviousness.

Furthermore, the Examiner has engaged in pure hindsight reconstruction. Fraser *et al.* disclose more than 1500 polypeptides from three *Neisserial* bacteria. The Examiner has asserted that it would be obvious to one of skill in the art to select the five currently claimed polypeptides from that set of 1500 polypeptides when there are more than 7,543,243,012,536,000 combinations of five polypeptides in Fraser *et al.* (1500 x 1499 x 1498 x 1497 x 1496). The vast majority of which would not provide the claimed scope of bactericidal activity. The Examiner has cited no

reason one of skill in the art would select the claimed combination from over seven quadrillion possible combinations. The Examiner merely cites to a case for the proposition that that it is obvious to combine two compositions which are taught to be useful for the same purpose. However, Fraser *et al.* do not teach utility of the disclosed polypeptides to provide the claimed bactericidal activity and neither does Comanducci *et al.* as they only teach bactericidal activity in ET-5 strains. Thus, there is no teaching of the disclosed compositions being useful for the claimed activity, so there would be no reason to select the exact five antigens as claimed.

Even if the Examiner has established a *prima facie* case of obviousness, the presently claimed invention produces a surprising result which is a secondary consideration sufficient to rebut any *prima facie* case of obviousness. Submitted herewith is Giuliani *et al.* which disclose results obtained with the presently claimed five antigens in a vaccine composition. The presently claimed invention with MF59 as an adjuvant as indicated in Figure 3 provides dramatic coverage across many strains. Even with alum as an adjuvant, the vaccine provides one hundred percent coverage across ET5 and A4 which is commensurate in scope as claimed. This is an unprecedented result. This application and the Giuliani *et al.* paper are in fact the first demonstration of reverse vaccinology pioneered by the inventor Rino Rappuoli, screening a genome for likely antigens and then carefully narrowing the list of candidates to that subset that when combined can provide this kind of broad coverage across *N. meningitidis* serogroup B. See *PNAS*, 103(29):10831-10833 (2006), submitted herewith.

Applicants respectfully request that the Examiner withdraw the rejection of claims 4-14 and 26 under 35 U.S.C. § 102(b).

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002100300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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